REVIEW ARTICLE

OVARIAN TUMORS

Ovarian Tumors

A Review

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THIS ARTICLE WILL REVIEW selectively recent progress in the pathology of ovarian tumors, with particular emphasis on those aspects that relate to the management of the patient. Steroid-biochemical and immunologic advances, newly developed diagnostic and therapeutic approaches, and animal experimentation have all contributed to the understanding of the biology of ovarian neoplasia, and will also receive brief consideration.

Among the more important advances in the field of diagnostic pathology have been the attempts by both the International Federation of Gynaecology and Obstetrics (FIGO) and the World Health Organization (WHO) to standardize the classification and nomenclature of ovarian tumors.[1,2] Previously, because of wide differences in terminology, not only throughout the world, but even within scientifically advanced countries such as the United States, it has been very difficult or even impossible to interpret epidemiologic data and compare the results of various types of therapy in cases of ovarian cancer.[3] This problem should be minimized by the worldwide adoption of a uniform classification and nomenclature such as that proposed by WHO. Simultaneously, FIGO, the International Union Against Cancer, and the American Joint Committee for Cancer Staging and End-Results Reporting have been cooperating to achieve a uniform method of staging ovarian cancer. Accurate staging, which reflects the pathology of the cancer *in vivo*, is essential for the selection of optimal therapy and is as important as a correct microscopic diagnosis in reporting the results of therapy. The WHO classification of ovarian tumors is presented in Table 1 and the FIGO staging system for ovarian cancer in Table 2.[4]

Common Epithelial Tumors

These tumors account for about two-thirds of all primary ovarian tumors, and their malignant form for almost 90% of all ovarian cancers. Most common epithelial tumors are thought to be derived from the so-called surface epithelium of the ovary, the direct descendent of the

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coelomic epithelium, or mesothelium, of the embryonic gonadal ridge. The latter lies in close proximity to the coelomic epithelium that invaginates to form the müllerian duct, so it is not surprising that when the surface epithelium of the mature ovary undergoes neoplasia, usually after it has penetrated the underlying stroma to form inclusion glands, it acquires the potential of its embryonic neighbor to differentiate into epithelia resembling those of müllerian duct derivatives. Thus, serous tumors recapitulate the epithelium of the fallopian tube; endometrioid tumors, that of the endometrium; and mucinous tumors, that of the endocervix.

A number of individual tumors that are customarily included within the common epithelial category may have origins other than the surface epithelium, but classifying them elsewhere would be impractical and confusing. An example of such a neoplasm is the Brenner tumor, which has occasionally been observed to arise in the region of the rete ovarii or to originate within a teratoma.[5] Likewise, two observations suggest that some mucinous tumors may be of germ cell rather than surface epithelial origin: a) At least 20% of them have a gastric or intestinal rather than an endocervical type of epithelium[6,7] and b) 5% of them are associated with dermoid cysts.[8] However, Fenoglio and her associates,[9] on the basis of ultrastructural studies, concluded that the presence of an intestinal type of epithelium in some of these tumors reflects a metaplasia of the surface epithelium as it undergoes neoplastic change.

Although common epithelial tumors often contain more than one epithelial cell type on both light and electron microscopic examination,[10] the great majority of them are characterized by an obvious predominance of a single cell type, which facilitates their placement in one or another of the first five categories listed in Table 1. Most undifferentiated carcinomas belong in the common epithelial group and are probably undifferentiated forms of serous or endometrioid carcinomas. The accurate identification of the cellular subtype of a common epithelial tumor is important, particularly when it is malignant, because differences in biology, gross pathology, bilaterality, manner of spread, prognosis, and indicated therapy exist from one cellular subtype to another.[11-14]

Common epithelial tumors have also been subclassified according to three features other than the identification of their epithelial elements: a) the relative proportions of their epithelial and stromal components; b) the locus of the epithelial proliferation (i.e., within glands or cysts, on the serosal surface of the tumor, or in both locations); and c) the degree of malignancy of the epithelial or rarely the stromal component. The benign Brenner tumor is the only cellular subtype in which the stromal com-

Table 1—Histologic Classification of Ovarian Tumors

I. Common "Epithelial" Tumors
  A. Serous tumors
    1. Benign
      a. Cystadenoma and papillary cystadenoma
      b. Surface papilloma
      c. Adenofibroma and cystadenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
      a. Cystadenoma and papillary cystadenoma
      b. Surface papilloma
      c. Adenofibroma and cystadenofibroma
    3. Malignant
      a. Adenocarcinoma, papillary adenocarcinoma, and papillary cystadenocarcinoma
      b. Surface papillary carcinoma
      c. Malignant adenofibroma and cystadenofibroma
  B. Mucinous tumors
    1. Benign
      a. Cystadenoma
      b. Adenofibroma and cystadenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
      a. Cystadenoma
      b. Adenofibroma and cystadenofibroma
    3. Malignant
      a. Adenocarcinoma and cystadenocarcinoma
      b. Malignant adenofibroma and cystadenofibroma
  C. Endometrioid tumors
    1. Benign
      a. Adenoma and cystadenoma
      b. Adenofibroma and cystadenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
      a. Adenoma and cystadenoma
      b. Adenofibroma and cystadenofibroma
    3. Malignant
      a. Carcinoma
        (1) Adenocarcinoma
        (2) Adenoacanthoma
        (3) Malignant adenofibroma and cystadenofibroma
      b. Endometrioid stromal sarcomas
      c. Mesodermal (müllerian) mixed tumors, homologous and heterologous
  D. Clear cell (mesonephroid) tumors
    1. Benign: Adenofibroma
    2. Of borderline malignancy (carcinomas of low malignant potential)
    3. Malignant: Carcinoma and adenocarcinoma
  E. Brenner tumors
    1. Benign
    2. Of borderline malignancy (proliferating)
    3. Malignant
  F. Mixed epithelial tumors
    1. Benign
    2. Of borderline malignancy
    3. Malignant
  G. Undifferentiated carcinoma
  H. Unclassified epithelial tumors
II. Sex Cord Stromal Tumors
  A. Granulosa-stromal cell tumors
    1. Granulosa cell tumor
    2. Tumors in the thecoma-fibroma group
      a. Thecoma

b. Fibroma
c. Unclassified

B. Androblastomas; Sertoli-Leydig cell tumors
1. Well differentiated
a. Tubular androblastoma; Sertoli cell tumor (tubular adenoma of Pick)
b. Tubular androblastoma with lipid storage; Sertoli cell tumor with lipid storage (folliculome lipidique of Lecene)
c. Sertoli-Leydig cell tumor (tubular adenoma with Leydig cells)
d. Leydig cell tumor; hilus cell tumor
2. Of intermediate differentiation
3. Poorly differentiated (sarcomatoid)
4. With heterologous elements

C. Gynandroblastoma
D. Unclassified

III. Lipid (Lipoid) Cell Tumors

IV. Germ Cell Tumors
A. Dysgerminoma
B. Endodermal Sinus Tumor
C. Embryonal Carcinoma
D. Polyembryoma
E. Choriocarcinoma
F. Teratomas
1. Immature
2. Mature
a. Solid
b. Cystic
(1) Dermoid cyst (mature cystic teratoma)
(2) Dermoid cyst with malignant transformation
3. Monodermal and highly specialized
a. Struma ovarii
b. Carcinoid
c. Struma ovarii and carcinoid
d. Others
G. Mixed forms

V. Gonadoblastoma
A. Pure
B. Mixed with dysgerminoma or other form of germ cell tumor

VI. Soft Tissue Tumors Not Specific to Ovary

VII. Unclassified Tumors

VIII. Secondary (Metastatic) Tumors

IX. Tumor-Like Conditions
A. Pregnancy luteoma
B. Hyperplasia of ovarian stroma and hyperthecosis
C. Massive edema
D. Solitary follicle cyst and corpus luteum cyst
E. Multiple follicle cysts (polycystic ovaries)
F. Multiple luteinized follicle cysts and/or corpora lutea
G. Endometriosis
H. Surface-epithelial inclusion cysts (germinal inclusion cysts)
I. Simple cysts
J. Inflammatory lesions
K. Parovarian cysts

ponent is typically preponderant; when it is in tumors of other epithelial cell types, the terms *adenofibroma* or *cystadenofibroma* are applicable. It is difficult to determine whether the stromal element in many common epithelial tumors is a true neoplastic component or reflects a reaction of the ovarian stroma to the proliferating epithelial cells.

One of the most important and controversial features of both the FIGO and the WHO classifications is the inclusion therein of a new category of tumors, those of borderline malignancy, also termed *carcinomas of low malignant potential.* The organizations separated borderline tumors from obviously invasive forms of common epithelial carcinoma because of their association with a high survival rate and their typically indolent course when they do behave in a malignant fashion; however, it is important to emphasize that they are fatal in a minority of the cases. These tumors are characterized by unusual proliferative activity on the part of the epithelial component but no obvious invasion of the stromal compartment. The epithelial proliferation is characterized by varying degrees of nuclear

Table 2—Stagegrouping for Primary Carcinoma of the Ovary*

Stage I	*Growth limited to the ovaries*
Stage Ia	Growth limited to one ovary; no ascites
(i)	No tumor on the external surface; capsule intact
(ii)	Tumor present on the external surface or/and capsule ruptured
Stage Ib	Growth limited to *both* ovaries; no ascites
(i)	No tumor on the external surface; capsules intact
(ii)	Tumor present on the external surface or/and capsule(s) ruptured
Stage Ic	Tumor either Stage Ia or Stage Ib, but with ascites† present or positive peritoneal washings.
Stage II	*Growth involving one or both ovaries with pelvic extension*
Stage IIa	Extension and/or metastases to the uterus and/or tubes
Stage IIb	Extension to other pelvic tissues
Stage IIc	Tumor either Stage IIa or Stage IIb, but with ascites† present or positive peritoneal washings.
Stage III	*Growth involving one or both ovaries with intraperitoneal metastases* outside the pelvis and/or positive retroperitoneal nodes.
	Tumor limited to the true pelvis with histologically proven malignant extension to small bowel or omentum
Stage IV	*Growth involving one or both ovaries with distant metastases*
	If pleural effusion is present there must be positive cytology to allot a case to Stage IV.
	Parenchymal liver metastases equals Stage IV.
Special category	*Unexplored cases which are thought to be ovarian carcinoma*

* Based on findings at clinical examination and surgical exploration. The final histology after surgery is to be considered in the staging, as well as cytology as far as effusions are concerned.

† Ascites is peritoneal effusion which in the opinion of the surgeon is pathologic and/or clearly exceed normal amounts.

atypicality and mitotic activity and by cellular stratification, particularly in the form of cellular buds that appear detached from the linings of the cysts or the serosal surface of the tumor. It is important to emphasize that the diagnosis of borderline malignancy is based on an examination of the ovarian tumor itself; neither the presence of implants on the peritoneum, which may even invade the underlying tissue, nor the rare occurrence of metastasis excludes classification in this category. Modifications of the diagnostic criteria, which are required within certain subtypes of common epithelial tumors, will be discussed subsequently.

Serous Tumors

The distinction between a tumor of borderline malignancy and an invasive carcinoma appears to be most meaningful within the category of serous tumors. Santesson and Kottmeier,[11] as well as Aure and his associates,[14] have reported strikingly higher 10-year and 20-year survival rates for serous borderline tumors than for serous carcinomas. The most interesting finding of these investigators has been that patients with Stages II and III borderline tumors do almost as well as those with Stage I neoplasia. This observation justifies retaining the concept of borderline malignancy in those cases in which the tumor has spread beyond the ovary. The unexpectedly favorable prognosis of the serous borderline tumor with peritoneal "implants" has raised the question whether the latter are true implants or result from an extraovarian metaplastic proliferation of mesothelial cells in the direction of tubal epithelium (endosalpingiosis).[15] Indeed, Parmley and Woodruff [16] have concluded that many of the common epithelial tumors of the ovary are only mesotheliomas, with "implants" reflecting a neoplastic field change in the peritoneal lining cells. Although such a viewpoint deserves careful consideration, it is preferable to retain the more specific terms such as *serous* and *endometrioid* for the ovarian tumors, since they differ in many respects from typical mesotheliomas. Although it is well known that the extraovarian pelvic peritoneum can differentiate into müllerian types of epithelium, there are at present no reliable guidelines by which the pathologist can distinguish true implants of ovarian borderline tumors from atypical foci of endosalpingiosis. There is much to be learned about the biology of serous borderline tumors. Santesson [17] studied a variety of architectural and nuclear characteristics of the epithelial component of a large series of these neoplasms but was unable to correlate his findings with the clinical course; he did not perform mitosis counts, but it seems improbable that they would be generally helpful because mitoses are uncommon in most of the cases.

Mucinous Tumors

The difference in behavior between borderline and invasive mucinous tumors appears to be significant, but not as great as that between the parallel forms of serous tumors. Thus, Santesson [18] reported a 68% 10-year survival rate for borderline mucinous tumors in contrast to only 34% for invasive forms; and Hart and Norris,[19] analyzing only Stage I cases, recorded a 96% survival in borderline cases, but only a 59% salvage in cases of carcinoma. The latter investigators pointed out the difficulty in the diagnosis of stromal invasion in many cases of mucinous neoplasia. This problem results from the fact that, unlike the serous tumors, which typically form large cysts, mucinous tumors are commonly characterized by the presence of small glands distributed throughout the stromal compartment. Such glands can be difficult to distinguish from truly invasive glands if their epithelial linings are atypical. Hart and Norris, therefore, proposed a set of differential-diagnostic criteria that appear to be more reliable than the determination of the presence or absence of invasion alone: 1) if there is unquestionable invasion, the tumor is classified as a carcinoma and 2) if invasion is uncertain, the diagnosis depends on the height of the atypical proliferating epithelium—if the epithelium is less than four cells in thickness, the tumor is borderline; if it is four cells or greater, a diagnosis of invasive carcinoma is made.

Endometrioid Tumors

The concept of endometrioid tumor of the ovary, which had been introduced in the 1920s by Sampson,[20] was revived by FIGO in 1961 and subsequently adopted by WHO. This designation applies to any ovarian tumor, the architectural features and cellular components of which resemble those of normal or neoplastic endometrial glands more closely than those of any other type of müllarian-epithelial derivative.[21] The resemblance to endometrial epithelium exists at an ultrastructural as well as a light microscopic level.[22] An origin of endometrioid tumors in endometriosis can be demonstrated in 5 to 10% of the cases, but is not essential for the diagnosis. In identifying malignant forms of this tumor the pathologist must recognize that some differences in architecture and cell type exist between endometrioid carcinomas of the ovary and carcinomas of the endometrium. Because of the great tendency of ovarian tumors to become cystic, a papillary growth is more often encountered in the ovary than in the uterine corpus. Also, since most endometrioid carcinomas probably arise directly from the surface epithelium rather than from endometriotic tissue, the patterns and cellular characteristics of the poorly differentiated forms may merge almost imperceptibly with those of other

common epithelial tumors, particularly the serous carcinomas, creating problems in differential diagnosis. In such cases the designation *endometrioid carcinoma* probably should be reserved for these tumors with a predominant differentiation in the direction of tubular glands, whereas tumors with an intermediate pattern should be classified as serous. The importance of distinguishing the endometrioid from the serous carcinoma is mainly related to the differences in their biologic behavior. Unlike the serous carcinoma, which is bilateral in two-thirds of the cases, if all stages are considered, the endometrioid carcinoma involves both ovaries in only one-third of the cases.[12] Also, the latter tends to remain localized to the ovary and pelvis for longer periods than the serous carcinoma, which has usually spread throughout the abdomen by the time of surgical exploration.[13] As a result of these differences, the prognosis and treatment of the two forms of cancer differ.

One interesting facet of the endometrioid carcinoma is its frequent association with a carcinoma of the uterine corpus, which has been reported in as high as 20% of the cases.[21] The relatively good prognosis of patients with this combination of tumors and the fact that the uterine carcinoma is often small and appears to arise *in situ* suggest strongly that in most cases the two neoplasms reflect independent primary growth, although it may be impossible to establish this in an individual case. Almost all endometrioid tumors are carcinomas, and all the subtypes that have been found in the uterine corpus have also been identified in the ovary, including adenocarcinoma, "secretory" adenocarcinoma, mucin-rich adenocarcinoma, adenoacanthoma, and adenosquamous carcinoma. Other types of endometrioid cancer also occur rarely in the ovary, such as carcinosarcoma,[23] malignant mesodermal mixed tumor,[23] endolymphatic stromal myosis,[21] stromal sarcoma,[21] and mesodermal (müllerian) adenosarcoma.[24] Benign endometrioid tumors are rarely encountered, usually in the form of adenomatous polyps within endometriotic cysts or endometrioid adenofibromas.[21] Finally, endometrioid tumors having the morphologic features of borderline neoplasia are seen from time to time, but clinicopathologic studies have not yet clearly established criteria by which they may be distinguished reliably from invasive carcinomas.

Clear Cell Tumors

The clear cell tumors of the ovary were at one time considered to be of mesonephric or mesometanephric origin, or at least to differentiate in the direction of mesonephric or metanephric derivatives,[25] but now these neoplasms are generally considered to be of müllerian nature,[26] and in the genital tract, of müllerian origin.[27,28] The evidence for the modern view of

their histogenesis is abundant. Clear cell type ovarian carcinomas are often admixed with endometrioid carcinomas [26] and are associated with pelvic and ovarian endometriosis significantly more often than are ovarian cancers of any other type even including the endometrioid carcinoma.[26,29] A number of examples of clear cell carcinoma have been reported to arise from the epithelium of an endometriotic cyst.[26] The rare clear cell carcinoma of the uterine corpus arises within the endometrium, where mesonephric remnants have never been observed, and may be intimately admixed with areas of typical endometrial adenocarcinoma.[28] More recently, the development of clear cell carcinoma has been reported in young females with vaginal adenosis of a müllerian type [27] as a consequence of prenatal exposure to diethylstilbestrol.[30] Finally, although occasional clear cell carcinomas, especially those composed entirely of clear cells, bear a strong resemblance to the renal cell carcinoma, most of them are distinctly different on both light and electron microscopic examination, with the short, blunt microvilli of the clear cell carcinoma bearing little resemblance to the long, slender microvilli making up the brush border of the renal cell carcinoma.[31-33] Where the clear cell and the hobnail cell—the two cell types most commonly encountered in clear cell carcinomas—belong in the spectrum of epithelia of müllerian origin is unknown, but they bear striking resemblances, at both light and electron microscopic levels, to glycogen-rich endometrial glandular cells and the hobnail cells of the Arias-Stella phenomenon, both of which may be seen during pregnancy.[32,33] Like endometrioid tumors, almost all clear cell tumors are carcinomas; it is possible that well-differentiated forms with an exclusive adenofibromatous pattern belong in the borderline category, but such tumors have been sufficiently rare that their biologic behavior has not yet been established. One very interesting aspect of the clear cell carcinoma of the ovary is that, despite its rarity (approximately 5% of all ovarian cancers), it is the type of ovarian tumor that has been reported most frequently in association with the paraendocrine syndrome of hypercalcemia.[34,35]

Brenner Tumors

The Brenner tumor is included in the common epithelial category because a) the pelvic peritoneum is capable of transitional epithelial metaplasia, b) the epithelial nests of the tumor have occasionally been demonstrated to be continuous with the ovarian surface, and c) the tumor contains mucinous epithelium lining glands or cysts in about a third of the cases and ciliated epithelium of serous type on rarer occasions. At an ultrastructural level both the transitional type epithelial cells that pre-

dominate in Brenner tumors and the less common mucinous cells resemble those encountered in the urinary bladder and its tumors, suggesting transitional cell metaplasia of the surface epithelium as the histogenesis of many of these neoplasms; there are also electron microscopic similarities between the epithelial component of the Brenner tumor and Walthard nests, which are also thought to arise as a result of transitional metaplasia of pelvic peritoneum.[36-38] Several recent publications have described borderline and malignant varieties of Brenner tumor,[39-41] which, according to the literature in general, account for less than 1% of all Brenner tumors; however, in an unselected series at the Massachusetts General Hospital, they accounted for 8%.[41] The borderline tumors are characteristically cystic rather than solid, with cauliflower-like papillomatous masses protruding into the cysts; the cysts and papillae are lined predominantly by a transitional type of epithelium that has an appearance similar to that of a Grade I papillary carcinoma of the urinary tract. Some authors prefer the term *proliferating*, or *proliferative*, to *borderline* Brenner tumor because although the microscopic pattern is that of proliferative, noninvasive growth, there has been no report of implantation or other evidence of clinical malignancy to date. However, the number of recorded cases has been small, and the follow-up has been short in many of them. The term *borderline* seems worth retaining for uniformity of nomenclature within the common epithelial category, but only with the understanding that clinical malignancy has not yet been demonstrated. The malignant (invasive) Brenner tumor typically has the appearance of an invasive transitional cell carcinoma but may contain mucinous or squamous elements as well. As in some cases of mucinous neoplasia, it may be difficult to distinguish between a borderline and a malignant Brenner tumor on the basis of invasion of the stroma alone. The Brenner tumor is typically characterized by small epithelial nests strewn throughout an abundant stroma, and the presence of atypical cytologic changes in these nests can make it impossible to establish the presence or absence of invasion. It may be that the degree of cytologic atypia will eventually prove to be a more useful criterion for determining the degree of malignancy just as in cases of mucinous tumors.

Undifferentiated Carcinomas

Undifferentiated carcinomas, which account for 5 to 15% of ovarian cancers, deserve special emphasis because they may have a pattern, at low powers of magnification, suggestive of a diffuse or insular form of granulosa cell tumor and are commonly misdiagnosed as such. However, the obviously malignant character of the nuclei, the frequent extensive spread

of the tumor within the abdomen, and the generally rapid clinical course of the undifferentiated carcinoma should deter one from such a misinterpretation because these features are rarely, if ever, associated with the granulosa cell tumor.

Staging and Pathological Evaluation of Ovarian Cancer

Since the great majority of ovarian cancers are of the common epithelial variety, it is appropriate to discuss clinical staging (Table 2) in relation to these tumors. It is axiomatic that the optimal therapy of any cancer depends on an accurate knowledge of its extent. It has become apparent recently, however, that those who have been treating ovarian cancer have not been fully aware of its manner of spread, and more thorough and careful clinical staging, in which the pathologist plays an important role, is now being widely advocated.

Although the spread of ovarian cancer to pelvic, paraaortic, and/or mesenteric lymph nodes has been recognized as a common finding at autopsy (approximately 75% of the cases) for many years,[42,43] such spread has generally been considered a late phenomenon in the course of the disease. Recently, however, it has been found that 12% of Stage I and Stage II ovarian cancers are associated with almost certain evidence of iliac or paraaortic lymph node involvement on lymphographic examination.[44] In view of the known frequency of false negative results for metastatic carcinoma with this technique, undetected involvement of these lymph nodes has been estimated to be present in an additional 20% or more of the cases, bringing the total percent of probable involvement into the range of 30 or more. In support of these findings, Knapp and Friedman[45] demonstrated lymph node metastases in 20% of cases of Stage I carcinoma of the ovary in which they removed or biopsied paraaortic and pelvic lymph nodes.

Another route of spread of ovarian cancer has been elucidated by investigators at the National Cancer Institute,[46] who found that 5 of 12 patients with what was initially considered to be Stage I or Stage II disease had, on laparoscopic examination within a month after the primary operation, peritoneal implants on the undersurface of the right leaf of the diaphragm, now considered one of the early sites of spread of this tumor. Thus, more refined methods of staging than used in the past reveal that many cases of ovarian cancer have been understaged and undertreated.

Optimal therapy of an ovarian cancer requires not only a careful gross examination of the operative specimen, adequate microscopic sampling, and an accurate and complete diagnosis by the pathologist, but also his

close cooperation with the gynecologist in determining the clinical extent of the disease. Accordingly, the gynecologist should provide the pathologist with biopsy specimens from areas of suspected or even possible spread of tumor, as well as ascitic fluid or peritoneal washings for cytologic examination. Adhesions of the tumor should be biopsied or their location identified on the operative specimen so that the pathologist can evaluate their possible neoplastic involvement by microscopic examination. Finally, the pathologist should investigate carefully the serosal surface of the specimen in search of tumor invasion. A final responsibility that cannot be overemphasized is grading in addition to typing of the tumor, since the degree of differentiation is of great importance in terms of prognosis and therapy, even independently of the clinical stage.[47]

Etiology of Ovarian Cancer

Except for unexplained variations in the incidence of ovarian cancer in different countries, which may be environmental rather than genetic in origin, and an apparently higher frequency of the disease in nulliparous women, epidemiologic investigations have yielded few clues to the causes of ovarian cancer.[48,49] Opinions on the causation of the common epithelial carcinomas have been speculative and largely uninvestigated by animal experimentation. The fact that the mesothelial lining of the ovary, in contrast to that of the testis, is a rich source of carcinomas has led to the suggestion that its repeated regeneration after monthly ovulation has a role in the development of these tumors.[50] It has also been emphasized that the highest incidence of an ovarian cancer that resembles the human common epithelial carcinomas, and particularly the serous type, has been found in the domestic fowl,[51] which produces eggs with great frequency; in contrast, animals that have estrus cycles with infrequent ovulation have few such tumors.[50] Furthermore, carcinomas similar to the spontaneous forms can be induced experimentally in the domestic fowl by maintaining it in a constant environment with 12 hours of fluorescent lighting daily, which results in rapid egg production.[52] It is obvious, however, that a physiologic event such as ovulation cannot be the sole explanation for ovarian cancer. Parmley and Woodruff[53] have speculated that carcinogens, introduced through the lower genital tract, possibly by vaginal douches, may have a role, and, indeed, one case in the literature has raised the possibility that beryllium, so introduced, was a factor in the development of a pelvic cancer that resembled a serous carcinoma of the ovary.[54] In view of the established association of pleural and peritoneal mesotheliomas with asbestos exposure and the fact that most common epithelial carcinomas of the ovary are ultimately of mesothelial origin, asbestos and

related chemicals have also come under suspicion.[55] Attempts to assess the role of asbestos in rabbits and guinea pigs,[56] however, have resulted only in the production of benign proliferative lesions of the ovarian surface epithelium. Talc has also been implicated in ovarian carcinogenesis, on the basis of its electron microscopic identification in 10 of 13 ovarian cancers,[57] but Yaker and Benirschke[58] were unable to find silicate crystals with meaningful frequency in a series of cases of ovarian cancer studied by light microscopy. The role of these and other substances in the etiology of ovarian cancer needs further exploration by epidemiologic investigations and animal experimentation.

Early Detection of Ovarian Cancer

Because of the fact that over two-thirds of ovarian cancers have spread beyond surgical control by the time of their discovery, one of the most promising approaches to reducing the high mortality of the disease has been a search for methods of detecting it at an early stage. Unfortunately, the annual pelvic examination is not the answer because an ovarian cancer may be impalpable on one such examination and palpable several months later at a time when inoperable spread may have already occurred. Laboratory approaches that are being investigated intensively at the present time involve the measurements of various antigens, antibodies, enzymes, and hormones. These include the cardioembryonic antigen,[59] the beta subunit of human chorionic gonadotropin,[60] the Regan isoenzyme of alkaline phosphatase,[60] specific tumor antigens and antibodies,[61,62] and various steroid hormones and their metabolites.[63] These studies are largely in their infancy, with investigators plagued by problems of purification of antigens, false negative results, the lack of specificity of positive results, and the question of how often the findings will prove to be positive in the early, treatable stages of the disease. In the postmenopausal woman the simple observation of a palpable adnexal mass, no matter how small,[64] and the finding of abnormal maturation of squamous cells in the vaginal smear[65] remain crude, but valuable clues to the possibility of ovarian cancer. Unfortunately, cul-de-sac puncture to obtain peritoneal fluid for cytologic examination has not proven practical as a screening method for this disease because of the high percentage of inadequate specimens (35%) and the low yield of ovarian cancers (1.2%) none of which were unsuspected clinically.[66]

Sex Cord-Stromal Tumors

Tumors in this category may be composed of a single type of cell or combinations of cells that resemble to varying degrees: 1) those of the

female and male endocrine apparatus (granulosa cells, theca cells, and their luteinized derivatives; Sertoli cells and Leydig cells) and 2) indifferent derivatives of the gonadal stroma, particularly cells having the appearance of fibroblasts; occasionally heterologous elements, such as cartilage and skeletal muscle, are additionally present in the male subgroup of these tumors. A morphologic as well as a physiologic overlap exists among the various tumors in the sex cord-stromal category. Although the neoplastic cells typically appear to function like their normal counterparts, there are enough exceptions to this generalization to make prediction of the endocrine state of the patient on the basis of the morphology of the tumor hazardous.

Granulosa Cell Tumors

The category of granulosa-stromal cell tumors includes those tumors that are composed of granulosa cells and/or stromal derivatives, which range from fibroblasts to cells resembling theca externa or theca interna cells. The many growth patterns of these cellular constituents have been amply described and illustrated in the literature. One recently recognized form of granulosa cell tumor is the juvenile type, which is encountered almost always in the first two decades but is occasionally seen at a later age.[67] It is characterized by a macrofollicular or a diffuse, sometimes disorderly, pattern of growth; often extensive luteinization of either or both the granulosa and theca cell elements; and hyperchromatic nuclei, which give the tumor a more malignant appearance than supported by its clinical behavior.

The granulosa cell tumor in general is of a low grade of malignancy, reflected by its indolent growth and infrequent recurrence, which is usually in the pelvis and/or lower abdomen. Often the recurrence is first recognized more than 5 years after the initial therapy; distant metastases are rare. Although Santesson and Kottmeier[68] were able to correlate a diffuse pattern of the tumor with a higher probability of recurrence, other investigators[69] have been unable to duplicate their results; certainly there is no justification for separating these tumors into benign and malignant subgroups on the basis of their microscopic appearance.

There has been considerable interest in the cellular source of the estrogens that are typically produced by granulosa cell tumors. It has been emphasized that those tumors containing theca cells are more apt to be associated with feminizing effects than pure or almost pure granulosa cell tumors, and that numerous histochemical reactions characteristic of steroid hormone–producing cells are typically positive in the theca cell component and negative in the granulosa cell component of these tumors.[71,72]

However, exceptions to both of these observations have been encountered. Furthermore, Ryan and his associates,[73] working with cell isolates, found that granulosa cells and theca cells are both capable of estrogen production *in vitro*; the latter are the richer source, but the two cells functioning synergistically secrete a greater amount than either alone. The *in vitro* as well as the tissue-culture approach to the problem, however, has been criticized by Amin *et al.*,[74] who emphasize that neither normal nor neoplastic unluteinized granulosa cells have the ultrastructural features of steroid hormone–producing cells. Occasional granulosa cell tumors produce androgens, virilizing the patient; it is curious that several of these have had a gross appearance that is most unusual for granulosa cell tumors in general, namely, that of a huge unilocular or multilocular thin-walled cyst resembling a serous cystadenoma.[75,76]

The origin of the human granulosa cell tumor is unknown; indeed, the embryologic origin of the normal granulosa cell is still disputed by embryologists, some tracing it to the coelomic epithelium and others to the mesenchyme (primitive stroma) of the gonadal ridge. Granulosa cell tumors and related neoplasms have been produced experimentally in rodents by a number of procedures, including total body irradiation,[77] the administration of radiomimetic substances such as triethylene melamine and myleran,[78] implantation of ovarian tissue into the spleen of castrated animals with resultant intrahepatic inactivation of estrogens,[79,80] and the administration of a carcinogen such as DMB (9,10-dimethyl-1,2-benzanthracene)[81] or a progestational steroid.[82] The major factors involved in tumor formation under these experimental conditions are thought to be destruction of ova and granulosa cells and high gonadotropin levels. There is a difference of opinion whether the induced tumors originate from the surface epithelium[77,82] or the stroma (interstitial cells) of the ovary.[79,83] Unfortunately, there are striking morphologic differences between the experimental and human tumors, and no clear-cut evidence exists for a role of either elevated gonadotropins or the destruction of ova or granulosa cells in the genesis of human cases, except for their high frequency after the age of 40 years. Very little investigation of the levels of the gonadotropins has been done in human cases of granulosa cell tumor.

Tumors in the Thecoma-Fibroma Group

Neither light nor electron microscopic examination permits a sharp distinction to be made between the ovarian fibroma, in which the stromal cells differentiate predominantly in the direction of collagen-producing fibroblasts, and the thecoma, in which differentiation is toward estrogen-producing theca cells.[84] Each of these tumors lies at the opposite end of a

spectrum of ovarian stromal cell neoplasia and only a biochemical approach can elucidate the nature of the intermediate forms with certainty. One recently recognized distinctive subtype within the previously unclassified category is the sclerosing stromal tumor, which has characteristic pathologic as well as clinical features.[85] On microscopic examination it presents a pseudolobular pattern in which cellular, often highly vascularized foci are separated by more extensive cell-poor collagenized, often edematous zones. A dual population of intimately admixed cells is encountered; some have the appearance of fibroblasts, while others contain large amounts of lipid and shrunken nuclei, resembling theca cells. Unlike the fibroma and thecoma, which are encountered in patients under the age of 30 years in less than 10% of the cases, sclerosing stromal tumors have been found in this age group in over 80% of 31 personally observed cases. These tumors, unlike thecomas, appear only occasionally to be associated with estrogen effects.[86]

Sertoli-Leydig Cell Tumors

Two terms are now in general usage for ovarian tumors that contain exclusively male cell types: *androblastomas* and *Sertoli-Leydig cell tumors*. The former designation emphasizes the fact that the more primitive tumors in this category may recapitulate, albeit imperfectly, the development of the testis, while the latter term focuses on the direction of differentiation of the neoplastic cells, even though such differentiation is realized only focally or to a minimal degree in some of the cases. The origin of these tumors is even more obscure than that of the granulosa-stromal cell tumors. Most, if not all ovaries contain male remnants in the form of rete ovarii and hilus cells (hilar-Leydig cells),[87] and these structures may provide a source for tumors of male cell type. It has also been shown, however, that Leydig cells, so identified because of their content of crystalloids of Reinke, can arise directly from the ovarian stroma, and tumors containing such cells can be situated within the ovary proper instead of its hilus.[88,89] Moreover, the granulosa cells of the graafian follicle, particularly in the dog, may form solid tubular structures that resemble closely testicular tubules containing Sertoli cells. These findings indicate that the specifically female compartment of the ovary may be a source of tumors composed of male cell types.

Just as granulosa cell tumors may be virilizing, so a number of tumors in the Sertoli-Leydig cell category have been associated with estrogenic manifestations. In view of the recent knowledge about the conversion of androgens to estrogens by peripheral tissues, particularly adipose tissue,[90] it is possible that the neoplastic cells in some of the reported cases of

"estrogenic" Sertoli-Leydig cell tumor have produced androgens that were converted to estrogens peripherally. On the other hand, there is evidence that both Leydig cells and Sertoli cells are capable of direct estrogen production. The evidence for estrogen secretion by testicular Leydig cells is strong in the human.[91] The association of pure Sertoli cell tumors of the canine testis[92] and the human testis and ovary[93] with estrogenic changes provides strong support for the ability of these cells to produce estrogens as well; also, isolated rat Sertoli cells have been shown to be capable of estrogen biosynthesis *in vitro*.[94]

The occasional occurrence of mucinous epithelium, argentaffin cells, carcinoid, rhabdomyoblasts, and islands of cartilage in Sertoli-Leydig cell tumors suggests the possibility of a germ cell origin when these elements are present, but gonadal tissues have never been reported in tumors of obvious germ cell origin, and the heterologous elements encountered in Sertoli-Leydig cell tumors do not resemble those most commonly observed in typical teratomas (i.e., skin, respiratory epithelium, neuroepithelium, and glia). It seems more probable, therefore, that the presence of these strange tissues reflects a metaplastic phenomenon.

In view of the fact that Sertoli-Leydig cell tumors show a range of morphologic variation as great as that of any tumor in the body with the exception of the teratoma, it is not surprising that electron microscopic examination of a small number of cases[95-101] has yielded many differing views of the nature of the cells and the histogenesis of the tumor. The subject has been confused further by the fact that two of the reports do not present convincing evidence that the tumors examined were correctly diagnosed by the accepted light microscopic criteria.[95,99] One report[100] describes ciliated cells lining the tubules of a mature Sertoli-Leydig cell tumor; these cells resembled those of the ductuli efferentes of the testis rather than Sertoli cells and were identified as corresponding to the former. However, the fact that the tubular elements of Sertoli-Leydig cell tumors appear to secrete estrogens in other cases suggests that such an interpretation cannot be valid for all the cases. Sertoli-Leydig cell tumors have been produced experimentally in the vestigial right ovary of the fowl by destruction of the functioning left ovary either by surgical removal or the intraovarian administration of P32.[102]

Mixed and Unclassified Sex Cord-Stromal Tumors

Because of the morphologic overlap between granulosa-stromal cell tumors and Sertoli-Leydig cell tumors, it is not uncommon on extensive sectioning of the former to find small foci that appear more characteristic of the latter, while the converse is true of Sertoli-Leydig cell tumors.

Occasionally these findings have been overemphasized in an attempt to create a separate entity of mixed sex cord-stromal tumor, or gynandroblastoma. Such a diagnosis should be avoided, however, unless there are significant quantities of mature, easily identifiable male and female elements within the same tumor; this finding has proven to be extremely rare and has no specific endocrine or other biologic association.

In about 10% of sex cord-stromal tumors it is impossible to be certain whether the cells and their patterns of growth are more typical of the female or the male gonad; in such cases, the term *sex cord-stromal tumor, unclassified* is used. One distinctive subtype within this category is the sex cord tumor with annular tubules (SCTAT),[103] which is characterized by simple and complex ring-shaped tubules, has a pattern intermediate between that of a granulosa cell tumor and a Sertoli cell tumor, and resembles a gonadoblastoma except for the absence of a germ cell component. The similarity to the gonadoblastoma also exists at an electron microscopic level in that the hyaline bodies within the annular tubules, like those of the gonadoblastoma, are composed of basement membrane material.[104] In contrast, typical Call-Exner bodies of a granulosa cell tumor are made up of an accumulation of cell fragments and amorphous material.[105] The SCTAT may be estrogenic, having been associated both with cystic hyperplasia of the endometrium[103] and isosexual precocity.[104] When it presents pathologically in the form of multiple tumors or tumorlets, the SCTAT is almost always complicated by calcification within the tubules and associated with the Peutz-Jeghers syndrome,[103] on occasion providing the first evidence of its existence. The tumor is encountered relatively frequently among sex cord-stromal tumors in the canine ovary.[106]

Lipid (Lipoid) Cell Tumors

Tumors composed exclusively of cells that have the typical appearance of steroid hormone–producing cells (i.e., lutein, Leydig, and adrenal-cortical cells), but possess no features that enable one to identify them specifically, have received the unfortunate designations *lipid* or *lipoid cell tumors*.[107] These terms are far from optimal, not only because of their lack of specificity, but also because tumors in this category may contain little or no lipid; a name such as *steroid cell tumor* might be more appropriate. Whenever lipid cell tumors, which may be androgenic or occasionally estrogenic or hormonally inactive, are encountered, all the available clinical, biochemical, histochemical, topographic, and histologic evidence should be evaluated in an attempt to make a diagnosis that is more precise. The possibilities to be considered in this situation are an adrenal

rest tumor, a hilus cell tumor, a nonhilar Leydig cell tumor, a stromal luteoma, or if the patient is pregnant, a so-called pregnancy luteoma.

If the tumor is in the broad liagment or ovarian hilus, an adrenal rest origin must be seriously considered because adrenal cortical rests have been identified in these sites in over 25% of hysterectomy and bilateral salpingo-oophorectomy specimens;[108] an intraovarian location of the tumor is evidence against such an origin because these rests have been found within the ovary with only exceptional rarity.[109] Although many virilizing ovarian tumors in the lipid cell category have been associated with one or more, but never all of the manifestations of Cushing's syndrome, such abnormalities are relatively common in the general population, and their presence alone is not convincing evidence of an adrenal rest origin. The strongest biochemical support for such a derivation of an ovarian tumor would be the demonstration of cortisol secretion, but this has not yet been clearly documented; also, in view of the atypical patterns of steroid hormone secretion by many endocrine neoplasms, even that finding might not be conclusive in the absence of confirmatory pathologic evidence. Therefore, although an adrenal rest tumor of the ovary is a distinct possibility, its existence has not yet been demonstrated, with the possible exception of 1 case in which the tumor synthesized cortisol and corticosterone *in vitro*.[110]

The only convincing support for the Leydig cell nature of a tumor of steroid cell type is the identification of crystalloids of Reinke in the cytoplasm of some of its cells. The absence of these structures, of course, does not exclude the diagnosis, in view of the fact that only 40% of Leydig cell tumors of the testis have been shown to contain crystalloids.[111] Most proven Leydig cell tumors of the ovary have arisen from hilus cells, but rare examples appear to have originated from ovarian stromal cells.[89] The specific diagnosis of hilus cell or Leydig cell tumor may be important clinically since such tumors have almost always been benign in contrast to nonspecific lipid cell tumors, which have proven to be malignant in more than one-fourth of the cases.[107] Tumors of Leydig cell origin tend to be associated with normal or only slightly elevated levels of urinary 17-ketosteroids because, unlike most virilizing tumors of adrenal cortical type, they produce predominantly the potent androgen testosterone, which is not a 17-ketosteroid, instead of the weaker androgens androstenedione and dehydroepiandrosterone,[112] elevations of which are typically associated with high values for urinary 17-ketosteroids.

Some tumors composed of steroid-type cells are small, lie within the ovarian stroma, and may be associated with foci of lutein cells elsewhere in the stroma of both ovaries, so-called stromal hyperthecosis, or luteinization of the stroma. It is logical to conclude that such tumors are composed

of luteinized stromal cells that have attained neoplastic proportions, warranting the designation *stromal luteoma.*[113] It is possible that many of the large tumors in the lipid cell category are also stromal luteomas, but when their topographic relations are obscured, it is impossible to identify them as such.

If the patient is pregnant, and single or multiple nodules of lutein-type cells are encountered in one or both ovaries, the diagnosis is almost certainly pregnancy luteoma(s).[114-116] These nodules are generally considered the result of lutein cell hyperplasia rather than true neoplasia. Pregnancy luteomas may be associated with virilization, but both their structural and their functional integrity are dependent on the pregnant state, as evidenced by their postpartum involution and loss of function. These nodules are multiple in at least half the cases; on microscopic examination they are composed of cells with abundant eosinophilic cytoplasm and little or no lipid, which are intermediate in size between granulosa-lutein and theca-lutein cells; the presence of frequent mitoses should not mislead one into making an erroneous diagnosis of malignancy.

If none of the above more specific diagnoses can be established on examination of a tumor composed of steroid-type cells, it must be placed in the nonspecific category of lipid cell tumor. It was anticipated at one time that with the availability of increasingly sophisticated assays of various steroid hormones, the cells of origin of endocrine neoplasms would be identifiable by their biochemical profile. Thus, it was expected that tumors of adrenal cortical–type cells would duplicate the characteristic hormone production of normal adrenal cortical cells, and hilus cell tumors that of normal Leydig cells. However, recent experience has shown that adrenal cortical adenomas can secrete testosterone instead of weak androgens,[117,118] whereas Leydig cell tumors, at least in the testis, can synthesize cortisol from precursors *in vitro.*[119] Likewise, responses to tropic hormones have been disappointingly inconstant and of dubious differential diagnostic value.[112,118] As a consequence, the morphology of a tumor must remain the basis for its classification until more accurate methods of establishing the nature of the neoplastic cells are devised.

Most lipid cell tumors are benign; except for a diameter of 8 cm or greater, no pathologic criteria have proven useful in predicting the occurrence of metastasis.[107]

Germ Cell Tumors

Because the various forms of germ cell tumor are often intermixed, careful gross examination and judicious sampling for microscopic study are necessary to achieve the complete diagnosis that is a prerequisite for

optimal therapy. Quantitation of the various components of a mixed germ cell tumor is also important in the determination of treatment and prognosis.[120]

Dysgerminoma

The dysgerminoma is composed uniformly of cells that resemble primordial germ cells morphologically, histochemically,[121] and ultrastructurally.[122] This tumor is identical in appearance to the testicular seminoma and primary germinomas of the anterior mediastinum and pineal region. It should be emphasized that the dysgerminoma may exist in the ovary in microscopic form; therefore, if such a tumor appears to be unilateral at operation and the opposite ovary is biopsied to exclude neoplastic involvement, detailed microscopic study of the biopsy specimen is warranted.

Several clinical and pathologic features of the dysgerminoma have been correlated with a tendency toward recurrence: an age less than 20 years; a diameter greater than 15 cm; intraoperative rupture; and the microscopic triad of a medullary architecture, anaplastic cells, and numerous mitoses.[123]

Embryonal Carcinoma and Endodermal Sinus Tumor

Although the terms *embryonal carcinoma* and *endodermal sinus tumor* have often been used interchangeably in the past for certain highly malignant epithelial forms of germ cell tumor of the ovary, a true embryonal carcinoma in the sense of a tumor with the typical patterns seen in the embryonal carcinoma of the adult testis is extremely rare in the ovary, where it may be associated with an elevated level of HCG and sexual precocity.[124] In contrast, the endodermal sinus tumor is remarkably similar morphologically to what has been called the infantile form of embryonal carcinoma (or orchioblastoma) of the testis;[111,125,126] it is more common than the embryonal carcinoma and is rarely accompanied by endocrine manifestations. It is important, therefore, to distinguish these two tumors in both gonads. The endodermal sinus tumor (yolk sac tumor) is characterized by a reticular pattern, characteristic papillary formations (Schiller-Duval bodies), and both intracellular and extracellular hyaline droplets.[126] Present evidence suggests that this tumor recapitulates predominantly extraembryonic rather than embryonic tissues, with its distinctive papillary units simulating endodermal sinuses, structures of yolk sac origin in the rat placenta that ramify in the extraembryonic mesenchyme. As in the yolk sac, it has been demonstrated by immunofluorescence techniques that α-fetoprotein is present in the neoplastic epithelium of the endoder-

mal sinus tumor as well as in the eosinophilic PAS-positive hyaline droplets that it secretes.[127] The most significant advance in the treatment of endodermal sinus tumors is the demonstration of their response to combination chemotherapy.[128] Vincristine, actinomycin D, and cyclophosphamide have been used most frequently in the treatment of these otherwise almost uniformly fatal tumors.

Polyembryoma and Choriocarcinoma

Both the polyembryoma, an extremely rare tumor that contains a large population of embryoid bodies,[129] and the choriocarcinoma,[130,131] which is almost always mixed with other forms of germ cell tumor, may be associated with the production of chorionic gonadotropin as well as other hormones of placental type; these tumors also appear to be sensitive to chemotherapeutic agents.

Teratomas

Teratomas are divided into three major categories: immature, mature, and monodermal and highly specialized. Their earlier subclassification as solid or cystic according to their gross appearance should be avoided because both immature and mature teratomas can be either predominantly solid or predominantly cystic, and the prognosis depends on their degree of differentiation rather than their gross appearance. The mature teratomas are secondarily divided into solid and cystic types because of the many characteristic and unusual features of the latter, which almost always appear in the form of a dermoid cyst. A number of authors[132,133] have now adopted with slight modifications the grading system of immature teratomas proposed by Thurlbeck and Scully[134] and have found a meaningful correlation between the grade and the prognosis. Robboy and Scully[135] recently reviewed 12 cases of mature glial implantation on the peritoneum associated with predominantly solid teratomas, which included both immature and mature forms. This complication does not seem to have a deleterious effect on the prognosis of the patient. These investigators, as well as others,[136] have also observed cases in which immature metastases of teratomas matured spontaneously or after what would ordinarily be considered inadequate therapy. Because of the relatively poor prognosis of the immature teratoma, combination chemotherapy has also been used recently not only to treat recurrent and metastatic disease, but also prophylactically after the removal of Stage I tumors.[137] Preliminary experience has suggested that such treatment may be highly effective.

The term *mature cystic teratoma* is the most accurate one for the entire group of mature teratomas that are predominantly cystic, but the great

majority of these are lined by epidermis with its appendages, justifying the more familiar designation *dermoid cyst*. Several malignant tumors of adult type have been reported to arise from the various constituents of dermoid cysts, but over 80% of these are squamous cell carcinomas; others have included adenocarcinomas, carcinoids, melanomas, and several types of sarcoma. Investigators have continued to be interested in the genesis of teratomas, and a recent study utilizing chromosome banding techniques has provided evidence that dermoid cysts have a parthenogenetic origin, arising from an ovum after the first meiotic division.[138]

Animal models of teratomas and teratocarcinomas (teratomas with embryonal carcinomas) have been discussed recently in this journal.[139] Benign teratomas can be produced by transplanting embryos that range widely in developmental age to extrauterine sites in mice, whereas a teratocarcinoma (teratoma plus embryonal carcinoma) develops only if the transplanted embryo is presomitic.

The monodermal and highly specialized teratomas form a fascinating group of neoplasms that range from the very rare retinal anlage tumor[140] to the struma and primary carcinoid.[141] The struma ovarii is often not recognized either clinically or on gross examination of the operative specimen by the pathologist, so that by the time the diagnosis is made, various investigative approaches are no longer possible. When the tumor has a gross appearance simulating that of the normal thyroid gland and is associated with a dermoid cyst, it should be easily recognizable as a struma. However, in many instances it is present in pure or almost pure form, appearing as a brown or greenish-brown multilocular or unilocular cystic mass filled with glairy fluid and easily mistaken for a mucinous cystadenoma. Strumas are rarely malignant and are only exceptionally associated with overt hyperthyroidism. Spread of the tumor may be in the form of benign implants on the peritoneum or metastases to the lungs, bone, and elsewhere in a pattern similar to that of a primary carcinoma of the thyroid gland.

Primary carcinoids of the ovary [141] usually occur in association with other teratomatous elements but may be seen in pure or almost pure form. The pure primary carcinoid may be difficult to distinguish from a metastasis,[142] but a number of features are helpful in the differential diagnosis. All the reported cases of the primary tumor have been unilateral whereas metastases are almost always bilateral. Primary carcinoids rarely spread beyond the ovary, but metastases to the ovary are almost always accompanied by the presence of metastases elsewhere, especially on the peritoneum and in the liver. Consequently, if the tumor is functioning, the 5-HIAA test on the urine is usually positive in the postoperative period or

several months later in a case of metastasis, but becomes negative after the removal of a primary ovarian carcinoid.

Primary ovarian carcinoids can be subdivided into four categories: those of insular (midgut) type, those of trabecular (hindgut or foregut) type, strumal (associated with a struma), and a very rare form developing within a Sertoli-Leydig cell tumor. About a third of the primary insular carcinoids are associated with the carcinoid syndrome, which disappears after the removal of the tumor, although cardiac damage, if present, may persist and result in the death of the patient; rarely the tumor recurs several years postoperatively. Primary trabecular carcinoids have not been associated with a recognizable endocrine syndrome; on occasion they have also recurred after a postoperative interval of several years.

The strumal carcinoid [143-145] is an interesting combination of typical struma and carcinoid, mainly of the trabecular type, which are usually intimately admixed. This type of tumor was at one time included among the cases of malignant struma ovarii in the literature, but none of them have behaved in a malignant fashion clinically. In a few of the cases of strumal carcinoid there has been evidence suggesting function on the part of the thyroid element of the tumor, but the carcinoid syndrome has not been reported. This combination tumor is of great theoretical interest for several reasons. It bears a morphologic resemblance to the medullary carcinoma of the thyroid gland with amyloid stroma, which may contain argentaffin cells and is associated rarely with the carcinoid syndrome. Indeed, in 1 reported case of strumal carcinoid,[146] amyloid was claimed to be present in the stroma on electron microscopic examination, but unfortunately was not illustrated at a sufficiently high magnification for the claim to be convincing. The intimate admixture of thyroid epithelium and argentaffin cells with the latter occasionally lining colloid-filled thyroid follicles provides a strong argument against the neuroectodermal origin of argentaffin cells and their inclusion in the APUD system.[147]

Tumors Associated With Abnormal Sexual Development

Several types of gonadal tumor have been found with unusual frequency in association with abnormal sexual development. Often these neoplasms have replaced the underlying gonad to such an extent that it is impossible to determine whether it had been an ovary, a testis, or an abnormal gonad of another type. Because most of these tumors occur in phenotypic females, they are generally considered in the category of ovarian neoplasia.

Although many examples of testicular tumors containing cells with the morphologic and physiologic properties of adrenal cortical cells have been

recorded in cases of the adrenogenital syndrome,[148] there has been only one report of such a tumor in the ovary.[110] Patients with testicular feminization, more appropriately designated the androgen insensitivity syndrome,[149] are phenotypic females with a 46 XY chromosome pattern and morphologically abnormal cryptorchid testes, which contain fetal-type tubules and Leydig cells, and often a cellular stroma resembling ovarian stroma. These patients are generally seen by gynecologists, usually because of primary amenorrhea or the development of an adnexal mass. The latter is most often a hamartoma composed of varying proportions of tubules, Leydig cells, and fibromatous tissue resembling that of an ovarian fibroma, but occasionally the mass is made up exclusively of solid tubules containing Sertoli cells; in such cases it can be appropriately designated a Sertoli cell adenoma. Less than 4% of patients with the androgen insensitivity syndrome have seminomas by the age of 30 years, and less than one-third of them have these tumors by the age of 50 years.[150] These findings justify the removal of the gonads after the completion of puberty.

Other phenotypic females with a Y chromosome, who usually have a 46 XY or a 45 X, 46 XY karyotype or some other form of mosaicism, may also harbor malignant tumors of germ cell type.[151,152] These patients include those with pure gonadal dysgenesis (bilateral streak gonads without the congenital stigmata of Turner's syndrome), mixed gonadal dysgenesis (a streak gonad on one side and a testis on the other), and occasionally male pseudohermaphroditism with dysgenetic testes. The most common type of tumor encountered in this group of patients is the gonadoblastoma.[153] This neoplasm is characterized by discrete nests containing germ cells indistinguishable from those of a dysgerminoma or seminoma and smaller cells with oval or round nuclei, suggesting immature Sertoli or granulosa cells; in about two-thirds of the cases, cells resembling Leydig cells without crystalloids, or lutein cells, are found in the stroma between the nests. A distinctive feature is the presence of dense, round hyaline bodies within the nests; on both light and electron microscopic examination [154] these structures differ from Call-Exner bodies, being composed of basement membrane material; occasionally they are continuous with hyalinized thickening of the basement membrane surrounding the nest. Calcification, usually beginning within the hyaline bodies, is encountered in two-thirds of the tumors and may be extensive. In half the cases the germ cells transgress the limits of the nests and invade the stroma in the form of a seminoma or dysgerminoma.[153] Thus, the gonadoblastoma can be divided into two types: a nonmetastasizing pure form, which can be regarded as an *in situ* variety of germ cell tumor, and a second type in which there is also an invasive germinoma, which has the capacity to metasta-

size. Occasionally a more highly malignant germ cell tumor, such as an embryonal carcinoma [155] or choriocarcinoma,[156] arises from the germinal element of a gonadoblastoma. The gonadoblastoma may secrete androgens, and there is evidence in occasional cases of estrogen production as well. Dysgerminomas and other types of malignant germ cell tumor may also be encountered in pure form in a patient with abnormal gonads. In such cases the possibility of an origin in a gonadoblastoma that was missed because of inadequate sampling or was destroyed by the malignant tumor must be considered.

Patients with abnormal gonads and a 45 X karyotype (the most common type found in Turner's syndrome) or a 46 XX karyotype (often encountered in cases of pure gonadal dysgenesis) rarely have gonadoblastomas or malignant germ cell tumors, and there are few well-documented examples of either in patients with true hermaphroditism, who most frequently have a 46 XX karyotype.[157,158]

Finally, it is important to emphasize that not all tumors composed of germ cells and sex cord elements are gonadoblastomas. Rare neoplasms containing these components, examples of which have been reported by Talerman,[159,160] may lack the distinctive features of the gonadoblastoma, such as its architectural pattern, the hyaline bodies, and the germinoma type of germ cells; such tumors are found typically in patients with normal karyotypes.

Tumors With Functioning Stroma

A unique biologic phenomenon that may be associated with a wide variety of ovarian tumors is stimulation of the stroma within or adjacent to the neoplasm to secrete steroid hormones. In these tumors, which have been called "tumors with functioning stroma" [161] it is not the neoplastic cell but the stroma that functions. Tumors in this category may be benign or malignant, and primary or metastatic;[162] they may produce estrogens, androgens, or even a progestagen.

Several explanations are possible for the stimulation of the stroma in these tumors. Rare examples contain syncytiotrophoblastic cells, which secrete chorionic gonadotropin [163,164] and stimulate the stromal cells within and around the tumor to luteinize and produce steroid hormones. Dysgerminomas containing these cells have been reported to be associated with both estrogenic and androgenic manifestations. A second type of ovarian tumor with functioning stroma produces virilization during pregnancy,[165,166] and in cases of this type there is abundant evidence that the associated circulating chorionic gonadotropin is an important factor in the stimulation of the stroma. This evidence includes a) the much more

common appearance of luteinization in the stroma of ovarian tumors during pregnancy than in its absence, b) the temporal relation of the virilizing phenomena and abnormal hormone levels to the pregnancy in a number of the reported cases (i.e., the appearance of masculinization during pregnancy and its regression after delivery in patients whose tumor was present before, during, and after the pregnancy),[166] and c) an *in vitro* study of one tumor that virilized a pregnant patient, which demonstrated the required presence of chorionic gonadotropin for testosterone synthesis by the tumor tissue.[167,168] However, most tumors with functioning stroma are encountered in nonpregnant patients and do not contain syncytiotrophoblastic cells. The factors involved in the stimulation of the stroma in such cases are unknown at the present time. Luteinization of the stroma and evidence of steroid hormone secretion are more commonly encountered in association with certain histologic types of ovarian tumor. For example, primary mucinous tumors have a luteinized stroma and apparently produce steroid hormones more commonly than serous neoplasms; germ cell tumors are only occasionally associated with luteinization of the stroma, and in such cases often only the stroma at the periphery of the tumor is so transformed; finally, among metastases to the ovary, those from the large intestine are most apt to be accompanied by stromal luteinization and steroid hormone production, whereas those from the breast rarely have such associations.[162] Although some authors have suggested that the luteinization is dependent primarily on the architecture of the tumor, with neoplasms containing small units of neoplastic cells being more apt to produce this phenomenon than those containing larger aggregates, such an explanation appears simplistic. It is more logical to relate the stromal luteinization and hormone production to some substance secreted by the neoplastic cells, and indeed, the recent evidence that a variety of malignant neoplasms may be associated with elevated plasma levels of the beta subunit of chorionic gonadotropin [169] raises the possibility that this hormone may be involved. Kurman [170] has demonstrated in one of our cases of a virilizing Krukenberg tumor that the neoplastic cells in the ovary reacted positively with an immunoperoxidase method for demonstrating the beta subunit of chorionic gonadotropin; a similar reaction, however, could not be obtained in several other cases of tumors with functioning stroma.

Although ovarian tumors associated with overt evidence of functioning stroma are relatively rare, it is possible that those secreting subclinical quantities of steroid hormones may be fairly common. For example, it is well known that 40 to 50% of postmenopausal women with ovarian cancer have an abnormal degree of cornification in their vaginal smears, sug-

gesting excessive estrogen secretion.[65] Likewise, a similar proportion of women with common epithelial tumors of the ovary have increased levels of total urinary estrogens, pregnanediol, or both.[63] These findings suggest that many tumors in those categories may secrete estrogens and/or progesterone, and microscopic examination of them has indicated that the most likely source of these hormones is the stroma of the tumor.[63] As a corollary, the possibility arises that the measurement of one or more steroid hormones or their metabolites may eventually serve as a screening test for ovarian cancer.

Conclusions

Although there has been considerable progress in formulating a classification of ovarian tumors that may attain wide usage and in delineating new types of these tumors, there has been relatively little new knowledge regarding the causation, diagnosis, or treatment of ovarian cancer. Obviously, new epidemiologic studies utilizing a standard classification, the study of ovarian cancer in animal models, and attempts to devise methods to detect it at an early stage are imperative for the reduction of the present high mortality rate of ovarian cancer.

References

1. International Federation of Gynaecology and Obstetrics: Classification and staging of malignant tumors in the female pelvis. Acta Obstet Gynaecol Scand 50:1–7, 1971
2. Serov SF, Scully RE, Sobin LH: International Histological Classification of Tumours, No 9. Histological Typing of Ovarian Tumours. Geneva, World Health Organization, 1973
3. Scully RE: The need for uniform terminology. Hum Pathol 4:602–603, 1973
4. DiSaia PJ, Morrow CP, Townsend DE: Synopsis of Gynecologic Oncology. New York, John Wiley & Sons, 1975, pp 11–12
4. Hertig AT, Gore H: Tumors of the Female Sex Organs, Part 3. Tumors of the Ovary and Fallopian Tube. Washington, DC, Armed Forces Institute of Pathology, 1961
6. Fox H, Kazzaz B, Langley FA: Argyrophil and argentaffin cells in the female genital tract and in ovarian mucinous cysts. J Pathol Bacteriol 88:479–488, 1964
7. Langley FA, Cummins PA, Fox H: An ultrastructural study of mucin secreting epithelia in ovarian neoplasms. Acta Pathol Microbiol Scand [A] 233:76–86, 1972
8. Beck RP, Latour JPA: Review of 1019 benign ovarian neoplasms. Obstet Gynecol 16:479–482, 1960
9. Fenoglio CM, Ferenczy A, Richart RM: Mucinous tumors of the ovary: Ultrastructural studies of mucinous cystadenomas with histogenetic considerations. Cancer 36:1709–1722, 1975
10. Robert DK, Marshall RB, Wharton JT: Ultrastructure of ovarian tumors. I. Papillary serous cystadenocarcinoma. Cancer 25:947–958, 1970
11. Santesson L, Lottmeier HL: General classification of ovarian tumors. Ovarian Cancer, UICC Monograph Series, Vol 11. Edited by F Gentil, AC Junqueira. New York, Springer-Verlag, 1968, pp 1–8.

12. Kottmeier HL: Surgical management— conservative surgery: Indications according to the type of the tumour.[11] pp 157–164
13. Kottmeier HL: Proposals for the standardization of the combined treatment of ovarian cancer.[11] pp 257–266
14. Aure JC, Hoeg K, Kolstad P: Clinical and histological studies of ovarian carcinoma: Long-term follow-up of 990 cases. Obstet Gynecol 37:1–9, 1971
15. Burmeister RE, Fechner RE, Franklin RR: Endosalpingiosis of the peritoneum. Obstet Gynecol 34:310–318, 1969
16. Parmley TH, Woodruff JD: The ovarian mesothelioma. Am J Obstet Gynecol 120:234–241, 1974
17. Santesson L: Personal communication, 1969
18. Santesson L: Cited by FT Kraus. Gynecologic Pathology, St. Louis, C.V. Mosby Co., 1967
19. Hart WR, Norris HJ: Borderline and malignant mucinous tumours of the ovary: Histologic criteria and clinical behavior. Cancer 31:1030–1045, 1971
20. Sampson JA: Endometrial carcinoma of the ovary, arising in endometrial tissue in that organ. Arch Surg 10:1–72, 1925
21. Scully RE, Richardson GS, Barlow JF: The development of malignancy in endometriosis. Clin Obstet Gynecol 9:384–411, 1966
22. Cummins PA, Fox H, Langley FA: An electronmicroscopic study of the endometrioid adenocarcinoma of the ovary and a comparison of its fine structure with that of normal endometrium and of adenocarcinoma of the endometrium. J Pathol Bacteriol 113:165–173, 1974
23. Dehner LP, Norris HJ, Taylor HB: Carcinosarcomas and mixed mesodermal tumors of the ovary. Cancer 27:207–216, 1971
24. Clement PB, Scully RE: Extra-uterine mullerian adenosarcoma. Am J Clin Pathol (In press)
25. Schiller W: Mesonephroma ovarii. Am J Cancer 35:1–21, 1939
26. Scully RE, Barlow JF: "Mesonephroma" of ovary: Tumor of müllerian nature related to the endometrioid carcinoma. Cancer 20:1405–1417, 1967
27. Herbst AL, Scully RE: Adenocarcinoma of the vagina in adolescence: A report of 7 cases including 6 clear cell carcinoma (so-called mesonephromas). Cancer 25:745–757, 1970
28. Kurman RJ, Scully RE: Clear cell carcinoma of the endometrium: An analysis of 21 cases. Cancer 37:872–882, 1976
29. Aure JC, Hoeg K, Kolstad P: Carcinoma of the ovary and endometriosis. Acta Obstet Gynecol Scand 50:63–67, 1971
30. Herbst AL, Ulfelder H, Poskanzer DC: Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 284:878–881, 1971
31. Okagaki T, Richard RM: "Mesonephroma ovarii" (hypernephroid carcinoma): Light microscopic and ultrastructural study of a case. Cancer 26:453–461, 1960
32. Silverberg SG: Ultrastructure and histogenesis of clear cell carcinoma of the ovary. Am J Obstet Gynecol 115:394–400, 1973
33. Salazar H, Merkow LP, Walter WS, Pardo M: Human ovarian neoplasms: Light and electron microscopic correlations. II. The clear cell tumor. Obstet Gynecol 44:551–563, 1974
34. Scully RE: Editorial Comment. Surv Pathol Med Surg 4:125–126, 1968
35. Ferenczy A, Okagaki T, Richart RM: Para-endocrine hypercalcemia in ovarian neoplasms: Report of mesonephroma with hypercalcemia and review of literature. Cancer 27:427–433, 1971
36. Cummins PA, Fox H, Langley FA: An ultrastructural study of the nature and origin of the Brenner tumor of the ovary. J Pathol 110:167–176, 1973
37. Bransilver BR, Ferenczy A, Richart RM: Brenner tumors and Walthard cell nests.

Arch Pathol 98:76–86, 1974
38. Roth LM: The Brenner tumor and the Walthard cell nest: An electron-microscopic study. Lab Invest 31:15–23, 1974
39. Pratt-Thomas HR, Kreutner A Jr, Underwood PB, Dowdeswell RH: Proliferative and malignant Brenner tumors of ovary. Gynecol Oncol 4:176–193, 1976
40. Miles PA, Norris HJ: Proliferative and malignant Brenner tumors of the ovary. Cancer 30:174–186, 1972
41. Hallgrimsson J, Scully RE: Borderline and malignant Brenner tumours of the ovary: A report of 15 cases. Acta Pathol Microbiol Scand [A] 233:56–66, 1972
42. Bergman F: Carcinoma of the ovary: Clinicopathological study of 86 autopsied cases with special reference to mode of spread. Acta Obstet Gynecol Scand 45:211–231, 1966
43. Julian CG, Goss J, Blanchard K, Woodruff JD: Biologic behavior of primary ovarian malignancy. Obstet Gynecol 44:873–884, 1974
44. Parker BR, Castellino RA, Fuks ZY, Bagshaw MA: The role of lymphography in patients with ovarian cancer. Cancer 34:100–105, 1974
45. Knapp RC, Friedman EA: Aortic lymph node metastases in early ovarian cancer. Am J Obstet Gynecol 119:1013–1017, 1974
46. Rosenoff SH, Young RC, Chabner B, Hubbar S, DeVita VT Jr, Schein PS: Use of peritoneoscopy for initial staging and posttherapy evaluation of patients with ovarian carcinoma. Symposium on Ovarian Carcinoma, National Cancer Institute Monograph 42. Edited by RC Young, JP Smith. Washington DC, US Government Printing Office, 1975, pp 81–86
47. Decker DG, Malkasian GD, Taylor WF: Prognostic importance of histologic grading in ovarian carcinoma.[46] pp 9–11
48. Berg JW, Baylor SM: The epidemiologic pathology of ovarian cancer. Hum Pathol 4:537–547, 1973
49. Lingeman CH: Etiology of cancer of the human ovary: A review. J Natl Cancer Inst 53:1603–1618, 1974
50. Fathalla MF: Factors in the causation and incidence of ovarian cancer. Obstet Gynecol Surv 27:751–768, 1972
51. Campbell JG: Some unusual gonadal tumors of the fowl. Br J Cancer 5:69–82, 1951
52. Wilson JE: Adenocarcinomata in hens kept in a constant environment. Poult Sci 37:1253, 1958
53. Parmley TH, Woodruff JD: The ovarian mesothelioma. Am J Obstet Gynecol 120:234–241, 1974
54. Gold C: A primary mesothelioma involving the rectovaginal septum and associated with beryllium. J Pathol Bacteriol 93:435–442, 1967
55. Newhouse ML, Berry G, Wagner JC, Turok ME: A study of the mortality of female asbestos workers. Br J Ind Med 29:134–141, 1972
56. Graham J, Graham R: Ovarian cancer and asbestos. Environ Res 1:115–128, 1967
57. Henderson WJ, Joslin CA, Turnbull AC, Griffiths K: Talc and carcinoma of the ovary and cervix. J Obstet Gynaecol Br Commonw 78:266–272, 1971
58. Yaker A, Benirschke K: A ten-year study of ovarian tumors. Virchows Arch [Pathol Anat Histol] 366:275–286, 1975
59. DiSaia PJ, Haverback BJ, Dyce BJ, Morrow CP: Carcinoembryonic antigen in patients with gynecologic malignancies. Am J Obstet Gynecol 121:159–168, 1975
60. Fishman WH, Ingles NR, Vaitukaitis J, Stolbach LL: Regan isoenzyme and human chorionic gonadotropin in ovarian cancer.[46] pp 63–69
61. Bhattacharya M, Barlow JJ: Tumor-associated antigen for cystadenocarcinomas of the ovary.[46] pp 25–32
62. Ioachim HL, Dorsett BH, Sabbath M, Barber HRK: Electronmicroscopy, tissue cultures, and immunology of ovarian carcinoma.[46] pp 45–62

63. Rome RM, Laverty CR, Brown JB: Ovarian tumors in postmenopausal women: Clinicopathological features and hormonal studies. J Obstet Gynaecol Br Commonw 80:984–991, 1973
64. Barber HR, Graber EA, Kwon TH: Ovarian cancer. CA 24:339–350, 1974
65. Rubin DK, Frost JK: The cytologic detection of ovarian cancer. Acta Cytol 7:191–195, 1963
66. Keettel WC, Pixley EE, Buchsbaum HJ: Experience with peritoneal cytology in the management of gynecologic malignancies. Am J Obstet Gynecol 120:174–182, 1974
67. Dickersin GR, Scully RE: The juvenile granulosa cell tumor: Report of 20 cases and review of the literature. Unpublished data
68. Kottmeier HL: Carcinoma of the Female Genitalia. The Abraham Flexner Lectures, Series No. 11. Baltimore, William & Wilkins Co., 1953
69. Norris HJ, Taylor HB: Prognosis of granulosa-theca tumors of the ovary. Cancer 21:255–263, 1968
70. Fox H, Agrawal K, Langley FA: A clinicopathologic study of 92 cases of granulosa cell tumor of the ovary with special reference to the factors influencing prognosis. Cancer 35:231–241, 1975
71. McKay DG, Robinson D, Hertig AT: Histochemical observations on granulosa cell tumors, thecomas and fibromas of the ovary. Am J Obstet Gynecol 58:625–639, 1949
72. Guraya SS: Histochemical study of granulosa and theca interna during follicular development, ovulation, and corpus luteum formation and regression in the human ovary. Am J Obstet Gynecol 101:448–457, 1968
73. Ryan KJ, Petro Z, Kaiser J: Steroid formation by isolated and recombined ovarian granulosa and thecal cells. J Clin Endocrinol 28:355–358, 1968
74. Amin H, Richart RM, Brinson AO: Preovulatory granulosa cells and steroidogenesis: An ultrastructural study in the rhesus monkey. Obstet Gynecol 47:562–568, 1976
75. Norris HJ, Taylor HB: Virilization associated with cystic granulosa tumors. Obstet Gynecol 34:629–635, 1969
76. Giuntoli RL, Celebre JA, Wu CH, Wheeler JE, Mikuta JJ: Androgenic function of a granulosa cell tumor. Obstet Gynecol 47:77–79, 1976
77. Furth J, Butterworth JS: Neoplastic diseases occurring among mice subjected to general irradiation with x-rays. II. Ovarian tumors and associated lesions Am J Cancer 28:66–95, 1936
78. Conklin JW, Upton AC, Christenberry KW: Further observations on late somatic effects of radiomimetic chemicals and x-rays in mice. Cancer Res 25:20–28, 1965
79. Biskind MS, Biskind GS: Development of tumors in the rat ovary after transplantation into the spleen. Proc Soc Exp Biol Med 55:176–179, 1944
80. Furth J, Sobel H: Neoplastic transformation of granulosa cells in grafts of normal ovaries into spleens of gonadectomized mice. J Natl Cancer Inst 8:7–16, 1947
81. Krarup T: Effect of 9,10-dimethyl-1,2-benzanthracene on the mouse ovary: Ovarian tumorigenesis. Br J Cancer 24:168–186, 1970
82. Lipschutz A, Inglesias R, Panasevich VI, Salinas S: Granulosa cell tumors induced in mice by progesterone. Br J Cancer 21:144–152, 1967
83. Myhre E: Ovarian morphology following long-term treatment with sex hormones and contraceptive steroids in mice. Acta Pathol Microbiol Scand [A] (Suppl) 233:67–75, 1972
84. Amin HK, Okagaki T, Richart RM: Classification of fibroma and thecoma of the ovary: An ultrastructural study. Cancer 27:438–446, 1971
85. Chalvardjian A, Scully RE: Sclerosing stromal tumors of the ovary. Cancer 31:664–670, 1973
86. Damjanov I, Drobnjak P, Grizelj V, Longhino N: Sclerosing stromal tumor of the

ovary: A hormonal and ultrastructural analysis. Obstet Gynecol 45:675–679, 1975
87. Sternberg WH: The morphology, androgenic function, hyperplasia and tumors of the human ovarian hilus cells. Am J Pathol 25:493–521, 1949
88. Sternberg WH, Roth LM: Ovarian stromal tumors containing Leydig cells. I. Stromal Leydig cell tumor and non-neoplastic transformation of ovarian stroma to Leydig cells. Cancer 32:940–951, 1973
89. Roth LM, Sternberg WH: Ovarian stromal tumors containing Leydig cells. II. Pure Leydig cell tumor, non-hilar type. Cancer 32:952–960, 1973
90. MacDonald PC, Rombaut RP, Siiteri PK: Plasma precursors of estrogen. I. Extent of conversion of plasma Δ^4-androstenedione to estrone in normal males and non-pregnant normal, castrated and adrenalectomized females. J Clin Endocrinol 27:1103–1111, 1967
91. Gabrilove JL, Nicolis GL, Mitty HA, Sohval AR: Feminizing interstitial cell tumor of the testis: Personal observations and a review of the literature. Cancer 35:1184–1202, 1975
92. Huggins C, Moulder PV: Estrogen production by Sertoli cell tumors of the testis. Cancer Res 5:510–514, 1945
93. Teilum G: Classification of testicular and ovarian androblastoma and Sertoli cell tumors. Cancer 11:769–782, 1958
94. Dorrington JH, Armstrong DT: Follicle-stimulating hormone stimulates estradiol-17 synthesis in cultured Sertoli cells. Proc Natl Acad Sci USA 72:2677–2681, 1975
95. Kempson RL: Ultrastructure of ovarian stromal cell tumors: Sertoli-Leydig cell tumor and lipid cell tumor. Arch Pathol 86:492–507, 1968
96. Berendsen PB, Smith EB, Abell MR, Jaffe RB: Fine structure of Leydig cells from an arrhenoblastoma of the ovary. Am J Obstet Gynecol 103:192–199, 1969
97. Jenson AB, Fechner RE: Ultrastructure of an intermediate Sertoli-Leydig cell tumor: A histogenetic misnomer. Lab Invest 21:527–535, 1969
98. Fiz G, Vital C, LeBlanc M, Leng J, Vincedau J, Leger H: Etude d'un cas d'arrhénoblastome: Avec examen en ultrastructure. Bord Med 4:2145–2149, 1971
99. Murad TM, Mancini R, George J: Ultrastructure of a virilizing ovarian Sertoli-Leydig cell: Tumor with familial incidence. Cancer 31:1440–1450, 1973
100. Kalderon AE, Tucci JR: Ultrastructure of a human chorionic gonadotropin-and-adrenocorticotropin-responsive functioning Sertoli-Leydig cell tumor (Type 1). Lab Invest 29:81–89, 1973
101. Roth LM, Cleary RE, Rosenfield RL: Sertoli-Leydig cell tumor of the ovary, with an associated mucinous cystadenoma: An ultrastructural and endocrine study. Lab Invest 31:648–657, 1974
102. Warner NE, Friedman NB, Bomze EJ, Masin F: Comparative pathology of experimental and spontaneous androblastomas and gynoblastomas of the gonads. Am J Obstet Gynecol 79:971–988, 1960
103. Scully RE: Sex cord tumor with annular tubules: A distinctive ovarian tumor of the Peutz-Jeghers syndrome. Cancer 25:1107–1121, 1970
104. Waisman J, Lischke JH, Mwasi LM, Digman WJ: The ultrastructure of a feminizing granulosa-theca tumor. Am J Obstet Gynecol 123:147–150, 1975
105. Gondos B, Monroe SA: Cystic granulosa cell tumor with massive hemoperitoneum: Light and electron microscopic study. Obstet Gynecol 38:683–689, 1971
106. Norris HJ, Garner FM, Taylor HB: Comparative pathology of ovarian neoplasms. IV. Gonadal stromal tumours of canine species. J Comp Pathol 80:399–405, 1970
107. Taylor HB, Norris HJ: Lipid cell tumors of the ovary. Cancer 20:1953–1962, 1967
108. Falls JL: Accessory adrenal cortex in the broad ligament: Incidence and functional significance. Cancer 8:143–150, 1955
109. Symonds DA, Driscoll SG: An adrenal cortical rest within the fetal ovary: Report of a case. Am J Clin Pathol 60:562–564, 1973
110. Motlík K, Stárka L: Adrenocortical tumour of the ovary: A case report with

particular stress upon morphological and biochemical findings. Neoplasma 20:97–110, 1973
111. Mostofi FK, Price EB Jr: Tumors of the Male Genital System. Atlas of Tumor Pathology, Second Series, Fascicle 8. Armed Forces Institute of Pathology, Washington DC, 1973
112. Judd HL, Spore WW, Talner LB, Rigg LA, Yen SSC, Benirschke K: Preoperative localization of a testosterone-secreting ovarian tumor by retrograde venous catheterization and selective sampling. Am J Obstet Gynecol 120:91–96, 1974
113. Scully RE: Stromal luteoma of the ovary: A distinctive type of lipoid cell tumor. Cancer 17:769–778, 1964
114. Sternberg WH, Barclay DL: Luteoma of pregnancy. Am J Obstet Gynecol 95:165–184, 1966
115. Krause DE, Stembridge VA: Luteomas of pregnancy. Am J Obstet Gynecol 95:192–206, 1966
116. Norris HJ, Taylor HB: Nodular theca-lutein hyperplasia of pregnancy (so-called "pregnancy luteoma"): A clinical and pathologic study of 15 cases. Am J Clin Pathol 47:557–566, 1967
117. Werk EE Jr, Sholiotn LJ, Kalejs L: Testosterone-secreting adrenal adenoma under gonadotropin control. N Engl J Med 289:767–770, 1973
118. Pittaway DE, Andersen RN, Givens JR: *In vitro* studies on an HCG responsive, testosterone secreting adrenal cortical adenoma. Steroids 22:731–745, 1973
119. Engel LL, Lanman G, Scully RE, Villee DB: Studies on an interstitial cell tumor of the testis: Formation of cortisol-^{14}C from acetate-1^{14}C^{1}. J Clin Endocrinol 26:381–392, 1966
120. Kurman RJ, Norris HJ: Malignant mixed germ cell tumors of the ovary: A clinical and pathologic analysis of 30 cases. Obstet Gynecol 48:579–589, 1976
121. McKay DG, Hertig AT, Adams EC, Danziger S: Histochemical observations on the germ cells of human embryos. Anat Rec 117:201–219, 1953
122. Lynn JA, Varon HH, Kingsley WB, Martin JH: Ultrastructural and biochemical studies of estrogen secretory capacity of a "nonfunctional" ovarian neoplasm (dysgerminoma). Am J Pathol 51:639–661, 1967
123. DeLima OA Jr: Disgerminoma do Ovario. Sao Paulo, 1966
124. Kurman RJ, Norris HJ: Embryonal carcinoma of the ovary: A clinicopathologic entity distinct from endodermal sinus tumor resembling embryonal carcinoma of the adult testis. Cancer 38:2420–2433, 1976
125. Teilum G: Endodermal sinus tumors of the ovary and testis: Comparative morphogenesis of the so-called mesonephroma ovarii (Schiller) and extraembryonic (yolk sac-allantoic) structures of the rat's placenta. Cancer 12:1092–1105, 1959
126. Teilum G: Classification of endodermal sinus tumour (mesoblastoma vitellinum) and so-called "embryonal carcinoma" of the ovary. Acta Pathol Microbiol Scand 64:407–429, 1965
127. Teilum G, Albrechtsen R, Norgaard-Pedersen B: Immunofluorescent localization of alpha-fetoprotein synthesis in endodermal sinus tumor (yolk sac tumor). Acta Pathol Microbiol Scand 82A:586–588, 1974
128. Smith JP, Rutledge F: Advances in chemotherapy for gynecologic cancer. Cancer 36:669–674, 1975
129. Beck JS, Fulmer HF, Lee ST: Solid malignant ovarian teratoma with "embryoid bodies" and trophoblastic differentiation. J Pathol 99:67–73, 1969
130. Wider JA, Marshall JR, Bardin CW, Lipsett MB, Ross GT: Sustained remissions after chemotherapy for primary ovarian cancers containing choriocarcinoma. N Engl J Med 280:1439–1442, 1969
131. Gerbie MV, Brewer JI, Tamimi H: Primary choriocarcinoma of the ovary. Obstet Gynecol 46:720–723, 1975

132. Norris HJ, Zirkin HJ, Benson WL: Immature (malignant) teratoma of the ovary: A clinical and pathologic study of 58 cases. Cancer 37:2359–2372, 1976
133. Nogales FF Jr, Favara BE, Major FJ, Silverberg SG: Immature teratoma of the ovary with a neural component ("solid" teratoma): A clinicopathologic study of 20 cases. Hum Pathol 7:625–642, 1976
134. Thurlbeck WM, Scully RE: Solid teratoma of the ovary: A clinicopathological analysis of 9 cases. Cancer 13:804–811, 1960
135. Robboy SJ, Scully RE: Ovarian teratoma with glial implants on the peritoneum: An analysis of 12 cases. Hum Pathol 1:643–653, 1970
136. Benjamin F, Rorat E: Solid ovarian teratoma with peritoneal and abdominal wall implants, progressive in vivo maturation, and probable cure. Gynecol Oncol 3:308–313, 1975
137. Smith JP, Rutledge F, Sutow WW: Malignant gynecologic tumors in children: current approaches to treatment. Am J Obstet Gynecol 116:261–270, 1973
138. Linder D, McCaw BK, Hecht F: Parthenogenetic origin of benign ovarian teratomas. N Engl J Med 292:63–66, 1975
139. Damjanov I, Solter D: Animal model of human disease: Embryo-derived teratomas and teratocarcinomas in mice. Am J Pathol 83:241–244, 1976
140. Hameed K, Burslem MRG: A melanotic ovarian neoplasm resembling the "retinal anlage" tumor. Cancer 25:564–567, 1970
141. Robboy SJ, Norris HJ, Scully RE: Insular carcinoid primary in the ovary: A clinicopathologic analysis of 48 cases. Cancer 36:404–418, 1975
142. Robboy SJ, Scully RE, Norris HJ: Carcinoid metastatic to the ovary: A clinicopathologic analysis of 35 cases. Cancer 33:798–811, 1974
143. Scully RE: Recent progress in ovarian cancer. Hum Pathol 1:73–98, 1970
144. Scully RE: Ovarian tumors of germ cell origin. Progress in Gynecology, Vol 5. Edited by SH Sturgis, M Taymor. New York, Grune & Stratton, 1970
145. Robboy SJ, Scully RE: Strumal carcinoid tumor of the ovary. Lab Invest 26:488, 1972 (Abstr)
146. Arhelger RB, Kelly B: Strumal carcinoid: Report of a case with electron-microscopical observations. Arch Pathol 97:323–325, 1974
147. Pearse AGE, Polak JM, Heath CM: Polypeptide hormone production by "carcinoid" apudomas and their relevant cytochemistry. Virchows Arch [Zellpathol] 16:95–109, 1974
148. Burke EF, Gilbert E, Uehling DT: Adrenal rest tumors of the testes. J Urol 109:649–652, 1973
149. Naftolin F, Judd HL: Testicular feminization. Obstetrics and Gynecology Annual 1973. Edited by RM Wynn. Englewood Cliffs, N.J., Prentice-Hall, 1973, pp 25–53
150. Manuel M, Katayama KP, Jones HW Jr: The age of occurrence of gonadal tumors in intersex patients with a Y chromosome. Am J Obstet Gynecol 124:293–300, 1976
151. Schellhas HF: Malignant potential of the dysgenetic gonad. Part I. Obstet Gynecol 44:298–309, 1974
152. Schellhas HF: Malignant potential of the dysgenetic gonad. Part II. Obstet Gynecol 44:455–462, 1974
153. Scully RE: Gonadblastoma: A review of 74 cases. Cancer 25:1340–1356, 1970
154. Mackay AM, Pettigrew N, Symington T, Neville AM: Tumors of dysgenetic gonads (gonadoblastoma): Ultrastructural and steroidogenic aspects. Cancer 34:1108–1125, 1974
155. Talerman A: Gonadoblastoma associated with embryonal carcinoma. Obstet Gynecol 43:138–142, 1974
156. Gallager HS, Lewis RP: Sequential gonadoblastoma and choriocarcinoma. Obstet Gynecol 41:123–128, 1973
157. McDonough PG, Byrd JR, Tho PT, Otken L: Gonadoblastoma in a true her-

maphrodite with a 46,XX karyotype. Obstet Gynecol 47:355–358, 1976
158. Van Niekerk WA: True hermaphroditism: An analytic review with a report of 3 new cases. Am J Obstet Gynecol 126:890–905, 1976
159. Talerman A: A mixed germ cell-sex cord stroma tumor of the ovary in the normal female infant. Obstet Gynecol 40:473–478, 1972
160. Talerman A: A distinctive gonadal neoplasm related to gonadoblastoma. Cancer 30:1219–1224, 1972
161. Morris JM, Scully RE: Endocrine Pathology of the Ovary. St. Louis, C.V. Mosby Co., 1958, pp 131–139
162. Scully RE, Richardson GS: Luteinization of the stroma of metastatic cancer involving the ovary and its endocrine significance. Cancer 14:827–840, 1961
163. Case Records of the Massachusetts General Hospital (Case 11-1972). N Engl J Med 286:594–600, 1972
164. Ueda G, Hamanaka N, Hayakawa K, *et al.*: Clinical, histochemical and biochemical studies of an ovarian dysgerminoma with trophoblasts and Leydig cells. Am J Obstet Gynecol 114:748–754, 1972
165. Verheoven ATM, Mastboom JL, Van Lousden HAIM, Van der Velden WHM: Virilization in pregnancy coexisting with an (ovarian) mucinous cystadenoma: A case report and review of the virilizing ovarian tumors in pregnancy. Obstet Gynecol Surv 28:597–622, 1973
166. Connor TB, Gavin FM, Levin HS, Migeon CJ, Martin LG: Gonadotropin-dependent Krukenberg tumor causing virilization during pregnancy. J Clin Endocrinol 28:198–214, 1968
167. Hamwi GJ, Byron RC, Besch PK, Vorys N, Teteris NJ, Ullery JC: Testosterone synthesis by a Brenner tumor. I. Clinical evidence of masculinization during pregnancy. Am J Obstet Gynecol 86:1015–1020, 1963
168. Besch PK, Byron RC, Barry RD, Teteris NJ, Hamwi GJ, Vorys N, Ullery JC: Testosterone synthesis by a Brenner tumor. II. In vitro biosynthetic steroid conversion of a Brenner tumor. Am J Obstet Gynecol 86:1021–1026, 1963
169. Braunstein GD, Vaitukaitis JL, Carbone PP, Ross GT: Ectopic production of human chorionic gonadotropin by neoplasms. Ann Intern Med 78:39–45, 1973
170. Kurman RJ: Unpublished data